Remarks

Claims 38-52 are pending. Claims 38, 41 and 46 have been amended. New claims 50-53 have been added. Claim 41 was amended to correct a typographical error, and claim 48 was amended to correct a grammatical error. Support for the amendments to claim 38 can be found in the specification at least at page 6, lines 19-20 (modulus at equilibrium of 200 kPa), page 4, lines 23-25 (swelling in aqueous solution), page 19, line 3 (covalently polymerizable), and page 17, lines 24-25 (ethylenically unsaturated), and in claim 1 as originally filed (hydrogel-forming material). New claims 50-52 depend from claim 38 and further specify that the composition contains at least one initiator. Support for new claims 50 and 51 can be found in the specification at least at page 18, lines 1-2. Support for new claim 52 can be found in the specification at least at page 24, lines 26-27. Support for new claim 53 can be found in the specification at least at page 10, lines 11-12.

The claimed compositions

The claims define compositions for the preparation of strong hydrogels suitable for the repair of tissue subject to high mechanical stress, such as cartilage, ligaments or tendons (see specification at page 1, lines 20-26, and page 2, lines 17-26). Applicants determined that such hydrogel materials should have certain properties, including low hydration swelling, high solids content, and a modulus of at least 200 kPa (see specification at page 5 lines 26, to page 6, line 21). These characteristics of the hydrogels are controlled by polymerizing a monomer in a concentration of at least 30%wt in the presence of a crosslinking macromer, which contains both

hydrophobic and hydrophilic groups. The macromer contributes to the strength of the gel by creating a network. The density of the crosslinks contributes to the strength of the gel; the higher the crosslink content in the gel, the stronger the gel is. The monomer contributes to the strength of the gels by increasing the solids content; the higher the monomer content in the initial composition, the higher the solids content in the gel, and the stronger the gel is. Thus the claimed subject material defines compositions for forming hydrogels with a modulus of at least 200 kPa.

Rejection Under 35 U.S.C. § 103

Claims 38-49 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,726,250 to Zajaczkowski ("Zajaczkowski '250"), in view of U.S. Patent No. 5,410,016 to Hubbell ("Hubbell"). Claims 38-49 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Zajaczkowski '250, in view of WO 98/12243 to Jarrett *et al.* ("Jarrett"). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Legal Standard

The U.S. Patent and Trademark Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967), *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would

bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d, 1780 (Fed. Cir. 1992). *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989). The Court of Appeals for the Federal Circuit warned that "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is ***rigorous*** application of the requirement for showing of the teaching or motivation to combine prior art references." *In re Dembiczak*, 175 F.3d 994 at 999 (Fed. Cir. 1999) (emphasis added). The references must themselves lead those of ordinary skill in the art to what is claimed, otherwise the claims are not obvious.

Zajaczkowski '250

Zajaczkowski '250 discloses pressure-sensitive adhesive materials formed from copolymers containing hydrophilic macromers with only one covalently polymerizable group and water soluble monomers (col. 3, lines 24-27). Pressure sensitive adhesives are in a fluid form; they do not form gels.

Zajaczkowski '250 observes that known materials did not function well as wound dressings and biomedical electrodes since the adhesive delaminated from the wound due to excessive moisture buildup within the adhesive (see col. 2, lines 1-7). Thus, Zajaczkowski '250 emphasizes the importance of forming an adhesive which does not absorb water, but instead transports water from the skin to the atmosphere while adhering to the skin.

To accomplish this purpose, Zajaczkowski '250 uses a macromer that differs from the macromer defined by the present claims; first, it does not contain hydrophobic regions in addition to hydrophilic regions and second, it contains only one not *at least two covalently*

polymerizable groups. Although it mentions the further covalent crosslinking of the materials, Zajaczkowski '250 recommends the use of **at most 2%** of crosslinker (col. 7, lines 5-8). Such low density of crosslinking is insufficient to form gels, let alone gels with a modulus of at least 200 kPa. Indeed, Zajaczkowski '250 particularly points out that its crosslinked copolymers may be used in solution form (see col. 8, lines 6 -8 and 37-40) and that the materials are pressure-sensitive and thus are fluids when subjected to force. Consequently, a skilled artisan would have no expectation that Zajaczkowski '250's materials would be capable of forming gels with a modulus of at least 200 kPa. Further, Zajaczkowski '250 does not provide, nor has the Examiner pointed to, any suggestion to modify its composition (or even just its macromer) so that it will have the properties defined by the claims, as amended.

Hubbell

Hubbell discloses how to make and use soft hydrogels. These hydrogels are formed essentially of polymerized macromers. If a monomer is present, only a minuscule amount is used (e.g. ~40ppm of vinylcaprolactam), which serves as an accelerant during the polymerization reaction (see col. 14, lines 38-45). These hydrogels are soft gels since they contain a very high proportion of water and minimal solids (see Table 7). The amount of water in these gels ranges from 82% (wt/wt) -94% (wt/wt). Hence, these hydrogels are most useful for soft tissue applications, such as reducing formation of adhesions after a surgical procedure, locally applying a biologically active substance to tissue surfaces, treatment or prevention of restenosis, abrupt reclosure, or vasospasm after vascular intervention (*see* col. 10, line 5 until col. 6, line 17).

Hubbell does not disclose or suggest how to render its gels stronger, so that they can withstand at least 200 kPa forces, and thus be suitable for repairs of tissue subject to mechanical stress. Further, Hubbell provides no motivation to modify its composition so that at least 30% (wt/wt) of the composition contains monomers and so that the composition is capable of forming gels with properties as defined by the claims.

The combination of Zajackowsi '250 and Hubbell

There is no teaching or suggestion in either of the references to combine Zajaczkowski '250 with Hubbell. Each reference is directed to monomers and macromers that are different from those described in the other reference. Each reference is directed to including amounts of the monomers and macromers in the composition that are different from the amounts disclosed in the other reference. And each reference is directed to forming compositions with different properties than the properties of the compositions disclosed in the other reference. For example, Zajaczkowski '250 specifically selects monomers and hydrophilic macromers with only one covalently polymerizable group to form adhesive, pressure-sensitive materials (*i.e.* liquids when exposed to force), while Hubbell uses macromers that contain hydrophilic and hydrophobic regions to produce soft hydrogels. Hubbell polymerizes the macromers with very small quantities of monomers that act as crosslinkers (*e.g.* 0.01 to 0.1 M; *see* col. 14, lines 40-41). If Zajaczkowski '250 contains covalent crosslinkers, only a miniscule amount is used. Hubbell's gels absorb large quantities of water and swell in the presence of water; while Zajaczkowski '250's materials are in the form of a liquid. Due to the different purposes for and properties

associated with the materials described by Zajaczkowsk'250 and those described by Hubbell, one of ordinary skill in the art would not substitute the hydrophilic macromers in Zajaczkowski '250 with the macromers in Hubbell.

Thus there is no disclosure or suggestion in Zajaczkowski '250 to replace its macromers with those described by Hubbell nor is there any disclosure or suggestion in Zajaczkowski '250 to form the hydrogels described by Hubbell. Therefore one of ordinary skill in the art would not combine these references.

However, even if one of ordinary skill in the art combined these references, it would not be obvious to produce the claimed compositions since neither reference discloses compositions that are capable of forming strong hydrogels with a modulus of at least 200 kPa. Zajaczkowski '250's macromer cannot not crosslink to form a gel; even if crosslinkers are added to the compositions, Zajaczkowski '250 includes the crosslinkers in such small quantities, that they are incapable of forming gels, let alone gels with a modulus of at least 200 kPa. Hubbell does not cure the deficiencies of Zajaczkowski '250. Hubbell discloses the formation of soft hydrogels, which are suitable for use in soft tissue applications, not tissue that will be subject to high mechanical stress. Thus, Hubbell does not disclose compositions that are capable for forming hydrogels with a modulus of at least 200 kPa. Therefore, the combination of Zajaczkowski '250 with Hubbell, would not disclose the compositions, as defined by the amended claims, to one of ordinary skill in the art. Thus, the claimed compositions, as amended, are not obvious over Zajaczkowski '250 in view of Hubbell.

Jarrett

Jarrett discloses the formation of soft gels that are elastic and compliant, and contain improved degradable functionalities. Jarrett discloses hydrogels that are formed from macromers containing at least one carbonate or dioxanone group, at least one water soluble block, and at least one polymerizable group (abstract). Optionally, like Hubbell '016 (above), Jarrett includes a very small amount of a comonomer, such as vinyl caprolactam (4,000 ppm) (page 39, lines 16-17). In contrast, the present claims require that at least 30% (wt/wt) of the composition contains a monomer. Jarrett's polymers are used as tissue sealants and coatings on tissue and medical devices (see page 7, lines 10-16; page 32, lines 1-18). These materials absorb a lot of water, are very elastic and have a low modulus (*see e.g.* Example 8, page 46, lines 1-14, which had a compressive modulus of only 32.4 kPa (0.0324 MPa) (page 47, Table 1)). When a material swells, its modulus decreases even further (e.g. it becomes more elastic). Thus, at equilibrium, the compressive modulus for Jarrett's materials would fall outside the claimed range. Jarrett does not disclose or suggest how to render its gels stronger so that they could withstand at least 200kPa forces.

Zajaczkowski '250 and Jarrett

There is no teaching or suggestion in the references to combine Zajaczkowski '250 with Jarrett. Each reference is directed to monomers and macromers that are different from those described in the other reference. Each reference is directed to including amounts of the monomers and macromers in the composition that are different from the amounts disclosed in the

other reference. And each reference is directed to forming compositions with different properties than the properties of the compositions disclosed in the other reference.

Zajaczkowski '250 specifically selects monomers and hydrophilic macromers to form adhesive, pressure sensitive materials. Upon polymerization, Zajaczkowski '250's macromers and monomers do not form a gel. Jarrett does not produce materials with the properties desired by Zajaczkowski '250. Jarrett discloses macromers that contain hydrophilic and hydrophobic regions and form gels upon polymerization. Further, Jarrett polymerizes the macromers with very small quantities of monomers that act as accelerants. Due to Jarrett's selection of macromers and minimal inclusion of monomers, Jarrett forms a hydrogel with a low modulus. In contrast, Zajaczkowski '250's selection of macromers with hydrophilic macromers containing only one covalently polymerizable group, and optionally including limited quantities of crosslinkers, results in materials that do not form gels when polymerized. Thus, due to the different purposes for and the properties associated with the materials described by Zajaczkowsk'250 and those described by Jarrett, one of ordinary skill in the art would not substitute the hydrophilic macromers in Zajaczkowski '250 with the macromers in Jarrett. Therefore, there is no disclosure or suggestion in Zajaczkowski '250 to replace its macromers with those described by Jarrett nor is there any disclosure or suggestion in Zajaczkowski '250 to form the hydrogels described by Jarrett.

However, even if one of ordinary skill in the art combined these references, it would not be obvious to produce the claimed compositions since neither reference discloses compositions

that are capable of forming gels with a modulus of at least 200 kPa. Zajaczkowski '250's macromer cannot not crosslink to form a gel; even if crosslinkers are added to the compositions, Zajaczkowski '250 includes the crosslinkers in such small quantities, that they are incapable of forming gels, let alone gels with a modulus of at least 200 kPa. Jarrett does not cure the deficiencies of Zajaczkowski '250. Jarrett discloses the formation of soft hydrogels, which are used as tissue sealants and coatings on tissue and medical devices. These materials have a very low modulus (*see e.g.* Example 8, page 46, lines 1-14, which had a compressive modulus of only 32.4 kPa, which is even lower at equilibrium). Thus, Jarrett does not disclose compositions that are capable for forming hydrogels with a modulus of at least 200 kPa. Therefore, the combination of Zajaczkowski '250 with Jarrett, would not disclose the compositions, as defined by the amended claims, to one of ordinary skill in the art. Thus, the claimed compositions, as amended, are not obvious over Zajaczkowski '250 in view of Jarrett.

Legal Standard regarding references to "Common Knowledge"

Should the Examiner maintain the rejection over the amended claims, Applicants respectfully request that the Examiner provide specific documentary support for the combination of the references. The rationale to combine or modify the prior art may be "expressly or impliedly contained in the prior art or it may be reasoned from knowledge available to one of ordinary skill in the art, established scientific principles, or legal precedent." MPEP 2144, *citing In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Generally, the Examiner ***must cite*** to documentary evidence to

support a conclusion based on general knowledge available to one of ordinary skill in the art. *See* MPEP 2144.03. In rare circumstances "official notice" without documentary evidence is permissible. These circumstances are limited to times "when the facts asserted to be well-known, or to be common knowledge in the art are capable of instant and unquestionable demonstration as being well-known." *Id.* (*e.g.* other references of record supported the noticed fact, or there was nothing or record to contradict the noticed fact). However, as discussed above, it was not well-known to replace the macromer described by Zajaczkowski '250 with the macromer described by Hubbell or the macromer described by Jarrett.

Reconsideration and allowance of claims 38-53, as amended, is respectfully solicited.

Respectfully submitted,

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RESPONSE TO OFFICE ACTION

Certificate of Facsimile Transmission

I hereby certify that this Amendment and Response to Office Action, and any documents referred to as attached therein are being facsimile transmitted on this date, June 14, 2004, to the Commissioner for Patents, U.S. Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450.

Gloria Miller

Date: June 14, 2004